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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,110	ZHU ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,15,16,20-22 and 48-57* is/are pending in the application.

4a) Of the above claim(s) *48,49,51 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,15,16,20-22,50 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-8,15,16,20-22 and 48-57* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The newly introduced claims introduce limitations as to what types of cells are affected by the claimed method. However, it is not clear how the new limitations limit the claimed method itself; e.g. how the desire to affect inflammatory cells affects the actual process steps of the method.

Further, claim 59 in particular would seem not to be further limiting, as it is not clear how the method of claim 1 could be operable on other than inflammatory cells.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8, 15, 16, 20-22, 50, and 53-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Bellgrau et al., WO 95/32627, cited by applicants.

Bellgrau et al. teach methods of using FAS ligand to suppress lymphocyte mediated immune responses, including inflammation (see claim 20). Use of soluble FAS ligand is disclosed at page 11, and treatment of MS is specifically disclosed at page 14. As MS is a disease of the CNS, the person of ordinary skill in the art reading the disclosure of Bellgrau et al. would immediately grasp that the administration for treatment of MS would be to the CNS, meeting the limitation of "behind the blood-tissue barrier of the immune privileged site". Accordingly, the claims, taken as a whole, are anticipated by the disclosure of Bellgrau et al.

Applicants arguments, filed 11/21/2003, have been fully considered but are not deemed persuasive. Applicants argue that FasL was known to be proinflammatory, and therefore that the prior art teaches against the invention, citing Ottonello et al., Rescigno et al. and Alderson et al. in support of their position. This argument has been fully considered but is not deemed persuasive. Bellgrau discloses at page 5 that FasL is responsible for the creation of an immune-

privileged site by Sertoli cells, that protected pancreatic islet cells from rejection. As can be seen from pages 10-11, Bellgrau fully appreciated the role of FasL in inducing apoptosis of T and B cells, as well as that resting lymphocytes are not killed by anti-Fas antibodies (which mimic FasL, and were used in the art to determine the role of Fas receptor prior to the isolation and identification of FasL). Accordingly, it would appear that Bellgrau was cognizant of the pleiotrophic nature of the effects of FasL. Applicants, in their argument, state that "The ability of soluble Fas ligand to inhibit inflammation is surprising, in part, because full-length Fas ligand was reported to have proinflammatory effects." Applicants argument is contrary to the specification at pages 4-6. Both the instant specification and the prior art indicate *not* that soluble FasL has different effect than full-length FasL, but rather that the effect of binding Fas receptor, using *either* type of molecule, is dependent upon the nature and physiological state of the target cells. It is specifically noted that the specification at page 2 discloses at paragraph [0006] that soluble FasL is preferred due to lower toxicity, rather than due to a biological effect distinct from full-length FasL. Similarly, although applicants argue that Bellgrau does not point to any functional differences between soluble and full-length FasL, neither does the instant specification; it remains that the effect of FasL administration is tied to the location and timing of administration, and not whether soluble or non-soluble Fas-L is administered. Regardless of whether the active agent is soluble or full-length, it exerts its action by binding to the Fas receptor. Finally, applicants allegations as to the conclusions of the ordinary artisan upon reading the Bellgrau disclosure are not supported by the Queen patent (cited in the rejection below), that specifically credits Bellgrau at column 2 as providing the basis for using FasL as an immunosuppressive drug. The Queen patent discloses and claims FasL fusion proteins that are disclosed to have lower toxicity than FasL alone, as they can be targeted to the desired tissues, and avoid non-desired apoptosis of non-target cells.

Claims 1, 3-8, 15, 16, 20-22, 50, and 53-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Queen et al., U.S. Patent Number 6,046,310, cited by applicants.

Queen et al. teach methods of using FAS ligand fusion proteins to treat autoimmune diseases, including MS; see column 5 lines 38-45 and column 9, at lines 15-20. As MS is a

disease of the CNS, the person of ordinary skill in the art reading the disclosure of Queen et al. would immediately grasp that the administration for treatment of MS would be to the CNS, meeting the limitation of "behind the blood-tissue barrier of the immune privileged site". Accordingly, the claims, taken as a whole, are anticipated by the disclosure of Queen et al.

Applicants arguments, filed 11/21/03, have been fully considered but are not deemed persuasive. Applicants argue that because the proteins of Queen were fusion proteins, that they fail to anticipate the claims. This argument has been fully considered but is not deemed persuasive because the limitation that the active agent is a FasL fragment devoid of other sequences is not supported by the specification. Nowhere does the specification define FasL fragment as excluding fusion proteins. In fact, at paragraphs [0067]-[0070], the specification indicates that FasL fragments may *be* fusion proteins, and the only working examples in the specification utilize a FasL fragment fused to a FLAG peptide. Therefore, reading the claims in light of the specification, the Examiner cannot agree that fusion proteins are excluded from the recitation "FasL fragment".

Advisory Information:

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Claims 59 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly introduced Claim 61 is drawn to a method of inhibiting inflammation within an immune privileged site in an animal comprising the delivery of soluble Fas ligand *prior to the onset* of inflammation within an immune privileged site. The only basis in the specification found by the Examiner for this claim is at page 3, which states that the method can be used to "prevent the development of acute EAE by eliminating activated autoreactive T cells and/or macrophages during their infiltration into the CNS." This is the only disclosure of administration *prior* to the onset of inflammation, and does not support the scope of claim 61, which is not limited to CNS, nor to EAE, acute experimental allergic encephalomyelitis. Written description of the claimed invention must be present in the specification as originally filed. The written description requirement of 35 U.S.C. § 112, first paragraph is not met by later claims to what might have been obvious over the original disclosure. It is noted that if claim 61 were amended so as to limit the claimed subject matter to that which is disclosed, that is, to "prevent the development of acute EAE by eliminating activated autoreactive T cells and/or macrophages during their infiltration into the CNS" , such a claim would be found to lack utility under 35 U.S.C. § 101, as there is no utility to preventing an experimentally induced condition.

Claim 61 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

As stated above, claim 61 is drawn to a method of inhibiting inflammation within an immune privileged site in an animal comprising the delivery of soluble Fas ligand *prior to the onset* of

inflammation within an immune privileged site. The specification discloses the claimed method only to "prevent the development of acute EAE by eliminating activated autoreactive T cells and/or macrophages during their infiltration into the CNS". As EAE is an experimental model system, there is no utility for preventing an experimentally induced condition. Accordingly, as the method, as drawn to such, lacks utility, there is accordingly no enablement of such.

With respect to the remainder of the scope of the claim, the specification does not present any enablement of such a method.

The nature of the invention is the inhibition of inflammation prior to the onset of said inflammation, within an immune privileged site. The state of the prior art is that is not generally recognized that it can be predicted when inflammation will occur, such that one of ordinary skill in the art would not be able to identify a patient in need of such treatment. There are no working examples in which inflammation was prevented or reduced prior to onset, nor is there direction or guidance by the inventor as to conditions under which inflammation would be expected and thus treatable by the claimed method. The only such guidance pertains to the prevention of EAE induced inflammation, which is easily predictable (just treat prior to inducing the condition), as the condition is by definition experimentally induced. However, said treatment of EAE is found to lack utility, for reasons cited above. Further, the specification at paragraph [0004] specifically states that "the upregulation of the Fas system in the CNS is an endogenous mechanism to resolve the CNS autoimmune inflammation. However, this upregulation occurs during the EAE course, *and has no effect in inhibition of the development of EAE*." (Emphasis added.) Accordingly, it is concluded that it would require undue experimentation to make or use the invention, that is, to determine how to identify one at risk of inflammation of an immuno-priveleged site prior to the onset of said inflammation, and therefore to practice the invention as it is claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz. ***Effective 1/21/2004, Dr. Kunz' telephone number is 571-272-0887.***

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

09/927110.2
2/6/04

Part III: Detailed Office Action

Claims 1, 3-8, 15, 16, 20-22, 50 and 53-57 and newly introduced claims 58-61 are under consideration.

The rejection of claims 1, 3, 6-8, 15, 16, 20-22, 50 and 55-57 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of applicants amendments to the claims.

Formal Matters:

Applicant is advised that should claims 20-22, 50 and 53-57 be found allowable, claims 1, 3-8, 15 and 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Rejections under 35 U.S.C. § 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 61 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.